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A doxorubicin-containing bioconjugate can be synthesized by the following method. Doxorubicin (4) is the most widely used of the anthracycline antibiotics, and is clinically useful against a broad spectrum of solid and hematological tumors. Like etoposide, doxorubicin appears to target topoisomerase II, ultimately leading to growth arrest and nonapoptotic cell death (Fornari et al., 1996; Ling et al., 1996). The clinical usefulness of doxorubicin is limited by nonspecific toxicity, especially cardiotoxicity. Thus, it would appear to be a particularly good candidate for selective delivery. This is confirmed by its frequent use in liposome-based methods (Hu et al., 1996; Longman et al., 1995; Hosada et al., 1995), as part of immunoconjugates (Johnson et al., 1995; Sivam et al., 1995), or in prodrug approaches (Svensson et al., 1995).

Doxorubicin conjugated to cobalamin, Co[SALEN] and other organocobalt complexes according to the following reaction schemes. For the synthesis bioconjugate 9a, the condensation of the daunosamine amino group with acyl-Co(III) complex 22 is performed. This reaction forms the 2-pyrroline ring in analogy to published routes using 4-iodobutyraldehyde and 5-iodo-2-pentanone.(9b) The acyclic tertiary amine derivative 9b is available from 4 via initial reductive amination with acetaldehyde, then alkylation of the resulting secondary amine with the mesylate 23 derived from 18. Alternatively, treatment of 4 with chloroformate 19 provides carbamate 9c. If alternative points of attachment are desired, hydrazone-linked derivatives such as 9d can be used using simple cobalamin alkyl hydrazides such as 24, obtainable from 23. The cleavage of these bioconjugates is shown in the reaction scheme below.